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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,811	06/29/2001	Thomas D. Madden	16303-008020	7024

500 7590 11/19/2003

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EXAMINER	
OSTRUP, CLINTON T	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/19/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,811	MADDEN ET AL.	
	Examiner	Art Unit	
	Clinton Ostrup	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10,11,13-15,17-21,23 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10,11,13-15,17-21,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-2, 4-8, 10-11, 13-15, 17-21, 23, and 26 are pending in this application.

Priority

Priority to U.S. Provisional Application Numbers 60/264,616, filed January 26, 2001, and 60/215,556 filed June 30, 2000 has been acknowledged.

Response to 37 CFR 1.132 Declaration

The declaration by Sean Semple, under 37 CFR 1.132 filed October 7, 2003 is sufficient to overcome the 35 U.S.C. 103(a) rejection of claims 1-2, 4-8, 10-11, 13-15, 17-21, and 23 as being unpatentable over Slater et al., 6,355,268 and further in view of NEXSTAR PHARMACEUTICALS INC., WO 99/13816.

Response to Applicant's Arguments/Amendment

Double Patenting

Applicants' request in Paper No. 17, filed October 7, 2003, that the Obviousness-Type Double Patenting rejection be held in abeyance is noted, however, all reasonable rejections are made. Applicants may hold their response to this rejection in abeyance until allowable subject matter has been indicated; however, the said rejection has been MAINTAINED for the reasons indicated in Paper No. 5, mailed July 22, 2002 and Paper No. 9, mailed April 7, 2003, as well as those found below.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-8, 10-11, and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-35, 37, 39-57, and 60-63 of copending Application No. 09/896,812. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to liposomal formulations comprising camptothecin and/or topotecan compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

Applicant's amendment filed October 7, 2003, Paper No. 14, to the rejection of claims 9 and 12 under 35 U.S.C. 112, second paragraph have made the rejection moot. Therefore, the said rejection has been withdrawn.

Claim Rejections - 35 USC § 103

Applicant's amendment and arguments filed October 7, 2003, Paper No. 14, to the rejection of claims 1-2 and 4-23 under 35 U.S.C. 103(a) have been fully considered and deemed persuasive. Therefore, the said rejection has been withdrawn.

New Claim Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Madden et al., Encapsulation of Topotecan in Lipid-Based Carrier Systems. Evaluation of Drug Stability and Plasma Elimination in a Murine Model, and Comparison of Antitumor Efficacy Against Murine L12210 and B16, Proc. Of ASCO, 17: abstract #754 (1998).

Madden et al teach a lipid-based carrier formulation which differs from earlier liposomes in that topotecan is trapped in the aqueous interior of the carrier. The reference teaches topotecan is stable in plasma and that even after 24 hours after injection, the topotecan remaining in the circulating carriers is almost 90% lactone. Therefore, Madden clearly teaches a liposomal topotecan formulation as claimed instantly in claims 6-7. See: abstract.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-5, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madden et al., Encapsulation of Topotecan in Lipid-Based Carrier Systems. Evaluation of Drug Stability and Plasma Elimination in a Murine Model, and Comparison of Antitumor Efficacy Against Murine L12210 and B16, Proc. Of ASCO, 17; abstract #754 (1998).

Madden et al teach a lipid-based carrier formulation which differs from earlier liposomes in that topotecan is trapped in the aqueous interior of the carrier. The reference teaches that the carrier is (sphingomyelin:cholesterol) and that encapsulation

of topotecan is at relatively high drug-to-lipid ratios (>0.1:1 mole/mole) and drug concentrations (for example 5mg/ml topotecan). See: abstract.

Therefore, the Madden et al reference teaches a liposomal topotecan formulation comprising a lipid, topotecan, sphingomyelin and cholesterol, as claimed instantly in claims 1-2, 4-5, and 23. While the reference is silent with respect to the specific dosage as claimed instantly in claims 1 and 5, differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.

Claims 1, 2, 4-5, 13-15, 17-21, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madden et al., Encapsulation of Topotecan in Lipid-Based Carrier Systems. Evaluation of Drug Stability and Plasma Elimination in a Murine Model, and Comparison of Antitumor Efficacy Against Murine L12210 and B16, Proc. Of ASCO, 17; abstract #754 (1998) and further in view of Ormrod et al., Topotecan: A review of its Efficacy in Small Cell Lung Cancer, Adis Drug Evaluation, Drugs 1999; Sep; 58(3); pages 533-551.

Madden et al teach a lipid-based carrier formulation which differs from earlier liposomes in that topotecan is trapped in the aqueous interior of the carrier. The reference teaches that the carrier is (sphingomyelin:cholesterol) and that encapsulation of topotecan is at relatively high drug-to-lipid ratios (>0.1:1 mole/mole) and drug concentrations (for example 5mg/ml topotecan). See: abstract.

The primary reference teaches that camptothecins have shown good anticancer activity and specifically tests liposomal encapsulated topotecan formulations comprising a lipid, topotecan, sphingomyelin and cholesterol, on murine leukemia and melanoma cell lines. The reference also teaches treating administering intravenously multiple doses of the formulation on days 1, 5, and 9. Therefore teaching the method steps of instant claims 18-20. See: abstract.

Although Madden et al teach a liposomal topotecan formulation comprising a lipid, topotecan, sphingomyelin and cholesterol, and the use of such formulations for the treatment of cancer, the reference lacks the treatment of the specific cancers claimed in claims 13-15, 17-21 and 26 and the amounts of topotecan as claimed in claims 1 and 17.

Ormrod et al teach that topotecan has antitumor activity against small cell lung cancer and ovarian cancer. The secondary reference teaches that in Phase II trials, topotecan was usually administered at 1.5mg/m2 for five days and that monotherapy of intravenous topotecan was administered at 1.5mg/m2 for five consecutive days every three weeks. See: page 534, paragraph 1- paragraph 3; page 540, col. 2, third full paragraph – page 541, col. 1, second full paragraph.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the liposomal formulation and method of using said formulation as taught by Madden et al by using the dosage amounts, and dosage schedule that was shown to be effective as taught by Ormrod et al, for the treatment of ovarian and small cell lung cancer because of the reasonable expectation of obtaining a

formulation containing an effective amount of topotecan and a method of administering said formulation in a liposomal formulation which has been shown to maintain the active lactone form of topotecan over a long period of time.

Claims 8 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madden et al., Encapsulation of Topotecan in Lipid-Based Carrier Systems. Evaluation of Drug Stability and Plasma Elimination in a Murine Model, and Comparison of Antitumor Efficacy Against Murine L12210 and B16, Proc. Of ASCO, 17; abstract #754 (1998) and further in view of Slater et al., 6,355,268.

Madden et al teach a lipid-based carrier formulation which differs from earlier liposomes in that topotecan is trapped in the aqueous interior of the carrier. The reference teaches that the carrier is (sphingomyelin:cholesterol) and that encapsulation of topotecan is at relatively high drug-to-lipid ratios (>0.1:1 mole/mole) and drug concentrations (for example 5mg/ml topotecan). See: abstract.

The primary reference teaches that camptothecins have shown good anticancer activity and specifically tests liposomal encapsulated topotecan formulations comprising a lipid, topotecan, sphingomyelin and cholesterol, on murine leukemia and melanoma cell lines. The reference also teaches treating administering intravenously multiple doses of the formulation on days 1, 5, and 9. See: abstract.

Although Madden et al teach a liposomal topotecan formulation comprising a lipid, topotecan, sphingomyelin and cholesterol, and the use of such formulations for the treatment of cancer, the reference lacks the divalent cation ionophore of instant claim 8.

Slater et al., disclose liposome-entrapped topoisomerase inhibitors including camptothecin and camptothecin analogs such as topotecan and irinotecan. See: col. 1, lines 42-52, col. 2, line 65 – col. 3, line 15. The secondary reference teaches that the liposome formulations remain in the blood stream for prolonged periods of time and retains the drugs antitumor activity. See: col. 2, lines 37-43 and abstract. The secondary reference teaches vesicle forming lipids in an amount between about 1-20 mole percent and having entrapped within the liposome a topoisomerase I/II inhibitor at a concentration of about 0.10-0.20 μmole drug per μmole lipid. See: col. 2, lines 45-64.

Slater et al., teach the vesicle-forming lipid as hydrogenated soy phosphatidylcholine, distearoyl phosphatidylcholine or sphingomyelin and other suitable lipids, including glycolipids and sterols such as cholesterol, can be used as vesicle forming lipids. See: col. 3, lines 30-68. The secondary reference teaches that the effective amount of the topoisomerase can vary depending on factors known to those skilled in the art and one skilled in the art would be able to consider such factors and make a determination regarding the effective amount. See: col. 5, lines 34-64.

The secondary reference teaches that encapsulation of camptothecin and its analogs, which have a α-hydroxy lactone ring which hydrolyzes in aqueous environments, is stabilized by entrapping these compounds in a liposome. Furthermore, Slater et al., specifically teach that the prior art has shown that a liposome-entrapped formulation of topotecan is stabilized and hydrolysis of the lactone ring is inactivated. See: col. 1, line 53 – col. 2, line 23. The secondary reference also teaches that a gradient can be produced by including a selected ionophore in the

liposomes and that said ionophore creates a lower inside/higher outside pH gradient. See: col.10, line 50 –col. 11, line 5.

The secondary reference teaches liposome-entrapped topotecan as being administered to animals as an intravenous bolus injection and the liposome-entrapped topotecan formulation as decreasing tumor volume and in some instances, complete remission of tumor mass. See: col. 16, line 49 – col. 18, line 33. The secondary reference describes how the liposome-entrapped topotecan has a significantly longer circulation time that the free form of the drug. Figures 4A and 4B show lipo-topotecan as remaining in the blood plasma in detectible concentrations for up to 72 hours post administration as compared to free topotecan remaining in the blood plasma in detectible concentrations for only about 2 hours post administration. See: col. 23, line 6 – col. 24, line 30.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the liposomal formulation of Madden et al by including a selected ionophore in the liposome formulation to create a lower inside/higher outside pH gradient because of the reasonable expectation of developing a liposome formulation which would be able to load high drug concentrations.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup
Examiner
Art Unit 1614

Frederick Krass
Primary Examiner
Art Unit 1614